PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Causes of infective endocarditis in the Western Cape, South Africa: A prospective cohort study utilising a set protocol for organism detection and central decision making by an Endocarditis team
AUTHORS	Pecoraro, Alfonso; Pienaar, Colette; Herbst, Philipus; Poerstamper, Simon; Joubert, Lloyd; Taljaard, Jantjie; Prozesky, Hans; Janson, Jacques; Newton-Foot, Mae; Doubell, Anton

VERSION 1 – REVIEW

REVIEWER	Ragnarsson, Sigurdur Skane University Hospital and Lund University
REVIEW RETURNED	25-Jul-2021

GENERAL COMMENTS	Overall: The authors describe the reduction of blood culture-negative infective endocarditis cases following the introduction of the Endocarditis Team and the employment of a systematic algorithm in organism detection in patients with infective endocarditis in a referral hospital in South Africa. The authors found a signicant reduction in blood culture-negative infective endocarditis and a reduction in mortality. The study compares a prospective cohort to a historical cohort. The study design seems to be well done. The results are clearly presented and the discussion is appropriate and relevant. I have a few concerns: Abstract: Page 4 Line 13: The authors state that the objective was „to identify the causes of infective endocarditis, in particular causes of BCNIE.“ I think this statement is too general does not accurately describe the aim of this paper. Rather, I would say that the authors assessed the impact of introducing a systematic approach in organism detection on the rate of BCNIE and in-hospital mortality. Introduction: No comments Methods: Page 7 Line 20. Clearly define the inclusion criteria. Did the patients need to fulfill the Modified Duke Criteria to be included?

	Line 27 How many patients were excluded? Were there no other exclusion criteria? Results: Page 10: Lines 49-51: Avoid using many decimals that do not affect the meaning of the result (use 0.96 instead of 0.955, use 0.98 instead of 0.981). Page 11 Lines 35 and 40: I suggest using ”viridans streptococci“ instead of “viridans group of streptococci“. Discussion: Page 12 Line 6: Delete the NODIE abbreviation. It is only used twice in the manuscript text. Lines 37-41: I agree with the authors that the reduction in in-hospital mortality is likely a true reduction. I think this is a type II statistical error due to a small sample size. However, the authors should be careful to draw conclusions based on this finding. The others can point out that the reduction in mortality may not have reached statistical significance due to type II statistical error. It is more appropriate to say that the introduction of an IE team may have played a role in the reduction in mortality rather than to say that it is likely. Tables: The tables lack footnotes with definitions af all abbreviations used in each table. Note that many of the numbers have commas instead of points to indicate decimals. Please use only points (dots) as decimal seperators.

REVIEWER	Suardi, Lorenzo Roberto Pisa University Hospital
REVIEW RETURNED	27-Jul-2021

GENERAL COMMENTS	The study I have been pleased to review has been performed accurately and provides interesting data from South Africa. I suggest minor revisions and I wish it could be published in order to enrich the scarce literature about blood-culture negative infective endocarditis. My minor revisions: Page 6 line 6: add to the references “Suardi LR, de Alarcón A, García MV, Ciezar AP, Hidalgo Tenorio C, Martinez-Marcos FJ, Concejo-Martínez E, De la Torre Lima J, Vinuesa García D, Luque Márquez R, Ojeda G, Reguera Iglesias JM, Lomas JM, Lopez-Cortes LE; Grupo para el Estudio de las Infecciones Cardiovasculares de la Sociedad Andaluza de Enfermedades Infecciosas (GEICV-SAEI). Blood culture-negative infective endocarditis: a worse outcome? Results from a large multicentre retrospective Spanish cohort study. Infect Dis (Lond). 2021 May

	26:1-9. doi: 0.1080/23744235.2021.1925342. Epub ahead of print. PMID: 34038316." Or, giving the huge data we provided with this study, please add a comment. Page 6 line 6 to 11: "It is important to note that the proportion of patients with BCNIE has decreased, which is likely due to a decrease in antibiotic use prior to blood culture collection": I think this sentence need more data to be justified because other recent studies did not agree on this. Page 6 line 25 to 30: add to the references "Suardi LR, de Alarcón A, García MV, Ciezar AP, Hidalgo Tenorio C, Martinez-Marcos FJ, Concejo-Martínez E, De la Torre Lima J, Vinuesa García D, Luque Márquez R, Ojeda G, Reguera Iglesias JM, Lomas JM, Lopez-Cortes LE; Grupo para el Estudio de las Infecciones Cardiovasculares de la Sociedad Andaluza de Enfermedades Infecciosas (GEICV-SAEI). Blood culture-negative infective endocarditis: a worse outcome? Results from a large multicentre retrospective Spanish cohort study. Infect Dis (Lond). 2021 May 26:1-9. doi: 0.1080/23744235.2021.1925342. Epub ahead of print. PMID: 34038316." Page 7 Patients with known or newly diagnosed malignancy were excluded from this study. Why did you choose to exclude this patients? Page 7 line 47-49 Additional imaging was performed at the discretion of the Endocarditis Team. Which kind? PET-TC, cardioTC? Page 10 in RESULTS paragraph: as the work is performed by Cardiologists, I would be interested to know which kind of " valvular heart disease" had the patients (about 30% reported) because, for example, bicuspid aortic valve is well known risk factor for BCNIE rather than BCPIE and Q-fever is associated. Please take a look and cite if you agree. Brouqui P, Dupont HT, Drancourt M, et al. Chronic Q fever.Ninety-two cases from France, including 27 cases without endocarditis. Arch Intern Med. 1993;153(5):642–648 Fenollar F, Fournier PE, Carrieri MP, et al. Risks factors and prevention of Q fever endocarditis. Clin Infect Dis. 2001; 33(3):312–316 OTHER COMMETS: • I would specifi Duke's modified criteria assessment in order to focus on POSSIBLE or DEFINITE endocarditis. Please add this data in the results. • About 32% of the patients (as shown in figure 3) with BCNIE did not receive a microbiological diagnosis.... I think a comment is due: how many of them went to surgery? Which criteria they had to be diagnosed with endocarditis?

	• No mention about Tropheryma whipplei as possible causative pathogen..what do you think about? Is it included in your PCR on valve tissue? • If possibile I would appreciate a logistic regression multivariate analysis on mortality In Tables 3 and 4 some percentage are missing

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
1. Abstract:
Page 4
Line 13: The authors state that the objective was to identify the causes of infective endocarditis, in particular causes of BCNIE. I think this statement is too general does not accurately describe the aim of this paper. Rather, I would say that the authors assessed the impact of introducing a systematic approach in organism detection on the rate of BCNIE and in-hospital mortality.
Changed to: “To assess the impact of a systematic approach to organism detection and identify the causes of infective endocarditis, in particular causes of BCNIE”.

2. Methods:
Page 7
Line 20. Clearly define the inclusion criteria. Did the patients need to fulfil the Modified Duke Criteria to be included?
We have added “by current criteria” to the reference.

3. Line 27 How many patients were excluded? Were there no other exclusion criteria?
One patient excluded due to pancreatic cancer; no other exclusion criteria were utilised.

4. Results: Page 10: Lines 49-51: Avoid using many decimals that do not affect the meaning of the result (use 0.96 instead of 0.955, use 0.98 instead of 0.981).
Updated.

5. Page 11: Lines 35 and 40: I suggest using ”viridans streptococci“ instead of “viridans group of streptococci“.
Accepted and changed.

6. Discussion: Page 12 Line 6: Delete the NODIE abbreviation. It is only used twice in the manuscript text.
Accepted and changed.

7. Lines 37-41: I agree with the authors that the reduction in in-hospital mortality is likely a true reduction. I think this is a type II statistical error due to a small sample size. However, the authors should be careful to draw conclusions based on this finding. The others can point out that the reduction in mortality may not have reached statistical significance due to type II statistical error.
We have added the following text to the limitations: ”The inability of this study to demonstrate a statistically significant in-hospital mortality benefit is likely due to the small sample size and thus a type II statistical error.”

8. It is more appropriate to say that the introduction of an IE team may have played a role in the reduction in mortality rather than to say that it is likely.
Changed to: “This reduction may be due to the introduction of an Endocarditis team (2) and the increased detection and subsequent effective treatment of the causative organism.”

9. Tables:
The tables lack footnotes with definitions of all abbreviations used in each table.
Updated.

10. Note that many of the numbers have commas instead of points to indicate decimals. Please use only points (dots) as decimal separators.
Updated.

Reviewer: 2

11. Page 6 line 6: add to the references “Suardi LR, de Alarcón A, García MV, Ciezar AP, Hidalgo Tenorio C, Martinez-Marcos FJ, Concejo-Martínez E, De la Torre Lima J, Vinuesa García D, Luque Márquez R, Ojeda G, Reguera Iglesias JM, Lomas JM, Lopez-Cortes LE; Grupo para el Estudio de las Infecciones Cardiovasculares de la Sociedad Andaluza de Enfermedades Infecciosas (GEICV-SAEI). Blood culture-negative infective endocarditis: a worse outcome? Results from a large multicentre retrospective Spanish cohort study. Infect Dis (Lond). 2021 May 26:1-9. doi: 0.1080/23744235.2021.1925342. Epub ahead of print. PMID: 34038316.” Or, giving the huge data we provided with this study, please add a comment.
Reference added.

12. Page 6 line 6 to 11: “It is important to note that the proportion of patients with BCNIE has decreased, which is likely due to a decrease in antibiotic use prior to blood culture collection”: I think this sentence need more data to be justified because other recent studies did not agree on this.
We have added references to the statement.

13. Page 6 line 25 to 30: add to the references “Suardi LR, de Alarcón A, García MV, Ciezar AP, Hidalgo Tenorio C, Martinez-Marcos FJ, Concejo-Martínez E, De la Torre Lima J, Vinuesa García D, Luque Márquez R, Ojeda G, Reguera Iglesias JM, Lomas JM, Lopez-Cortes LE; Grupo para el Estudio de las Infecciones Cardiovasculares de la Sociedad Andaluza de Enfermedades Infecciosas (GEICV-SAEI). Blood culture-negative infective endocarditis: a worse outcome? Results from a large multicentre retrospective Spanish cohort study. Infect Dis (Lond). 2021 May 26:1-9. doi:

0.1080/23744235.2021.1925342. Epub ahead of print. PMID: 34038316."
Added.

14. Page 7 Patients with known or newly diagnosed malignancy were excluded from this study. Why did you choose to exclude this patients?
We believed that malignancy may influence the mortality rate; only one patient was excluded due to malignancy.

15. Page 7 line 47-49 Additional imaging was performed at the discretion of the Endocarditis Team. Which kind? PET-TC, cardioTC?
PET-CT and cardiac MRI was performed.

16. Page 10 in RESULTS paragraph: as the work is performed by Cardiologists, I would be interested to know which kind of "valvular heart disease" had the patients (about 30% reported) because, for example, bicuspid aortic valve is well known risk factor for BCNIE rather than BCPIE and Q-fever is associated. Please take a look and cite if you agree.
Brouqui P, Dupont HT, Drancourt M, et al. Chronic Q fever.Ninety-two cases from France, including 27 cases without endocarditis. Arch Intern Med. 1993;153(5):642–648
Fenollar F, Fournier PE, Carrieri MP, et al. Risks factors and prevention of Q fever endocarditis. Clin Infect Dis. 2001;
33(3):312–316
The analysis of the underlying valvular abnormality and its association with specific causative organisms is part of a subgroup analysis of the prospective cohort and is currently under review.

17. OTHER COMMENTS: I would specify Duke's modified criteria assessment in order to focus on POSSIBLE or DEFINITE endocarditis. Please add this data in the results.
Added in table 1.

18. About 32% of the patients (as shown in figure 3) with BCNIE did not receive a microbiological diagnosis.... I think a comment is due: how many of them went to surgery? Which criteria they had to be diagnosed with endocarditis?
Criteria have been added to text and table 1. In terms of patients without a microbiological diagnosis, 5/9 patients underwent surgery, with IE confirmed by pathological criteria in all patients. In terms of clinical criteria, 3/9 were classified as definite IE and 6/9 classified as possible IE.

9. No mention about Tropheryma whipplei as possible causative pathogen. What do you think about? Is it included in your PCR on valve tissue?
Tropheryma whipplei is detectable by the 16S rRNA PCR that was performed on valve tissue. T. whipplei was not detected in any of the samples. We have clarified the testing protocol in the supplementary document.

20. If possible I would appreciate a logistic regression multivariate analysis on mortality.
We have consulted with our statistician, given the relatively small sample size with low event rate we are unable to demonstrate a statistical significant difference in mortality between the two cohorts.

21. In Tables 3 and 4 some percentage are missing.
Corrected.

VERSION 2 – REVIEW

REVIEWER	Ragnarsson, Sigurdur Skane University Hospital and Lund University
REVIEW RETURNED	04-Oct-2021

GENERAL COMMENTS	The authors have adressed my concerns adequately. I have nothing to add.

REVIEWER	Suardi, Lorenzo Roberto Pisa University Hospital
REVIEW RETURNED	15-Sep-2021

GENERAL COMMENTS	I think the authors tried to fix (and they succeded) the most important issues my revision was focused on. Therefore for me it is ok now.